

Remarks

This paper amends claims 1, 30 and 52. Support for the amendments is found in Table 1. No new matter is added by these amendments. After the amendments set forth herein are entered, claims 1-4, 6-17, 30-56 are pending and under examination.

The current claim amendments substitute the specific organic acids recited in Table 1 in place of the reference in the claims to Table 1. These amendments should be entered because no new search or examination is required and the amendments reduce the issues on appeal.

Objections of claims

The objection of claims 1-4, 6-8, 30-36 and 46-56 for incorporation of Table 1 into the claims, is respectfully traversed by the instant amendments. This objection should be withdrawn.

Rejection of claims under 35 U.S.C. § 102(b)

Claims 1-3, 6-8 and 46 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Gleispach et al. (Neuroblastoma Screening: Labeling of HVA and VMA for Stable Isotope Dilution Gas Chromatography-Mass Spectrometry, Supplement to Nutrition, Vol. 11, No. 5, 1995). Applicant respectfully traverses this rejection.

In asserting this rejection, the Examiner alleges that Figure 1 of Gleispach et al. provides a method for measuring the amount of an unlabeled organic acid using a structurally similar ¹⁸O-labeled organic acid as a standard. Specifically, the Examiner alleges that Gleispach et al. teach the use of ¹⁸O vanillylmandelic acid (VMA). The Examiner's understanding of this reference is in error.

Gleispach et al. teaches the preparation of deuterated VMA as an internal standard. In particular, Gleispach et al. provide a substitution reaction between unlabeled VMA and D₂O to effect VMA labeling. Gleispach et al. at p. 606, left column ("Synthesis of Labeled VMA"). Gleispach et al. did not attempt ¹⁸O-labeling of VMA (or any other organic acid) and states that

“an exchange of the carboxylic ^{16}O against ^{18}O was not attempted because alpha fragmentation prevents an intense signal of the molecular ion.” Gleispach et al., at p. 606, right column (emphasis added). Thus, because Gleispach et al. did not produce or use any ^{18}O -labeled organic acid, Gleispach et al. cannot anticipate the instant claims. Accordingly, this rejection is traversed and should be withdrawn.

Rejections of claims under 35 U.S.C. § 103(a)

Rejection of claim 4

The rejection of claim 4 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Gleispach et al. in view of Shushan et al. (US 2002/0019056), is respectfully traversed. The Examiner alleges that Gleispach et al. teaches every element of claim 4 except for the using liquid chromatography-mass spectrometry (LC-MS) for detection. To remedy this deficiency, the Examiner alleges that Shushan et al. teaches that “LC and GC are art-recognized equivalents and it would have been obvious to replace mass spectrometry detection using gas chromatography with liquid chromatography in order to obtain predictable results.” Office Action, page 5, item 13. Applicant respectfully disagrees.

As discussed above, Gleispach et al. does not teach using one or more oxygen-18 labeled organic acids for the measurement of the structurally similar or identical unlabeled organic acid. Furthermore, Gleispach et al. actually dissuades the artisan from attempting to use ^{18}O -VMA as alleged by the Examiner. As noted above, Gleispach et al. did not even attempt to produce ^{18}O -VMA because of the observed alpha fragmentation of the unlabeled (^{16}O -) compound. Shushan et al. fails to remedy this deficiency because none of the organic acids measured by Shushan et al. comprise an oxygen-18 label. This rejection is traversed and should be withdrawn.

Rejection of claims 9-15, 17 and 54-56

The rejection of claims 9-15, 17 and 54-56 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Gleispach et al. in view of Shaw (US 5,686,311), is respectfully traversed.

The Examiner alleges that Gleispach et al. teaches every element of the instant claims except for the adding to a sample an amount of at least one oxygen-18 labeled organic acid selected from each of hydroxyl mono-acid, dihydroxy mono-acid, dicarboxyl organic acid, hydroxyl dicarboxyl acid, tricarboxyl acid, glycine conjugate and keto acid. To remedy this deficiency, the Examiner alleges that Shaw teaches that “each of these groups hydroxy mono-acid, dihydroxy mono-acid, dicarboxyl organic acid, hydroxyl dicarboxyl acid, tricarboxyl acid, glycine conjugate and keto acid when found in abnormal amounts, can be used to demonstrate a diagnosis of autism.” Office Action, page 5, item 14. Applicant respectfully disagrees.

As discussed above, Gleispach et al. does not teach using any of the claimed oxygen-18-labeled organic acids for the measurement of the structurally similar or identical unlabeled organic acid. In fact, Gleispach et al. admits that it was not technically feasible to produce ¹⁸O-VMA. Shaw fails to cure this deficiency of Gleispach et al. None of the Shaw measurements of the organic acids comprise oxygen-18 labeled organic acids. Thus, the cited prior art fails to establish a *prima facie* case of obviousness because every element of the claimed invention is not taught or suggested.

This rejection is also deficient because nothing in the combination of Gleispach et al. and Shaw motivate the artisan to use multiple ¹⁸O-labeled organic acids, let alone one representative from each of the groups specified in claim 9 (step (a)). The Supreme Court in KSR Int’l Co. v. Teleflex Inc. held that rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. KSR Int’l Co. v. Teleflex Inc., 127 S.Ct. 1727, 1741 (2007) (quoting In re Kahn, 441 F.3d 977, 988, 78 U.S.P.Q.2d 1329, 1336 (Fed. Cir. 2006)). Thus, in order to establish a *prima facie* case of obviousness, it is necessary for the Examiner to identify the reasons why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed. Id. In this case, the rejection offers no rationale, supported by the cited prior art, for why the artisan is motivated to use more than a single ¹⁸O-labeled organic acid. The view that it is obvious to the artisan to use multiple ¹⁸O-labeled

organic acids is based solely on personal opinion without any factual basis in the prior art or other rational underpinning. Office Action at page 6. In sum, the cited prior art does not provide a motivation to combine and modify the methods in the manner alleged, providing a second independent basis for traversal of this rejection.

For the reasons discussed above, Applicant respectfully submits that the *prima facie* case of obviousness is deficient and should be withdrawn.

Rejection of claim 16

The rejection of claim 16 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Gleispach et al. and Shaw as applied to claim 9, further in view of Shushan et al., is respectfully traversed. As discussed above, Gleispach et al. and Shaw do not render obvious the invention of claim 9 because they fail to teach or suggest the use of the mixture of ¹⁸O-labeled organic acids recited in the claims. Shushan et al. is cited by the Examiner merely for teachings related to LC-MS and GC-MS. Thus, Shushan et al. does not remedy the deficiency in the combination of Gleispach et al. and Shaw discussed above. This rejection is traversed and should be withdrawn.

Rejection of claims 30-45

Claims 30-45 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Gleispach et al. in views of Breakefield et al. (US 5,030,570). The Examiner alleges that Gleispach et al. teaches every element of the instant claims except for the diagnosing the existence of a metabolic defect in an individual. To remedy this deficiency, the Examiner alleges that Breakefield et al. teaches that “abnormally low levels of VMA in urine demonstrate a metabolic defect in an individual.” Office Action, page 7, item 17. Applicant respectfully traverses this rejection.

As discussed above, Gleispach et al. does not teach using one or more oxygen-18 labeled organic acids for the measurement of the structurally similar or identical unlabeled organic acid and the Examiner has cited to no other art to teach this limitation. Breakefield et al. fails to cure

this deficiency of Gleispach et al. None of the Breakefield et al. measurements of the organic acids comprise oxygen-18 labeled organic acids, nor is it cited by the Examiner for this purpose. Breakefield et al. therefore does not provide what Gleispach et al. lacks. This rejection is traversed and should be withdrawn.

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Prompt and favorable action on the application is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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